Mandelic Acid in the Treatment of Urinary Infections

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IN view of the general acceptance of mandelic acid therapy by the medical profession and, because of the relative paucity of space devoted to discussion of this important therapeutic advance in the current medical journals on this side of the Atlantic, I respectfully submit this paper. The striking clinical results attendant on the use of this drug in urinary infections are vaguely, though generally pretty well known. There is always a strong flow tide of enthusiasm whenever a new drug is first used successfully, but only too often does the ebb tide of criticism and failure sweep this same treatment, only a short time before hailed as a panacea, out to the sea of disrepute and discard. In order to avoid such a sad state of affairs all new drugs should be thoroughly investigated and successfully tested clinically before they are placed on the market; this day of the high pressure "baronial" drug houses makes this ideal condition almost impossible.

The cure of severe urinary infections, especially the chronic ones, has always been a thorn in the side of the medical profession. It has been a problem against which their repeated efforts have been, much like Quixote's combat with the windmills, of little or no avail. Although there have been a vast number of urinary antiseptics on the market for years, they have been of but little aid, in fact their number bespeaks their inefficiency.

In order to understand the rationale and application of mandelic acid therapy, one should be conversant with the fundamental principles of the ketogenic diet, on which it has been developed. Before discussing these, one must define a few terms and their usage. Pyelonephritis is an inflammation of the kidney pelvis and is always accompanied by an inflammation of the kidney. Pyelitis is the term usually employed to describe this state, and, though a misnomer, will be used hereafter in this connection, because of its widespread, long continued usage and for brevity. It will be noted that the lower the pH the greater the acidity of the urine. Neutrality in action is represented by a pH of 7.0. The term, "cure of a urinary infection", is used in this article only when the urine becomes sterile to culture.

THE KETOGENIC DIET

Discovery:

Ever since Shohl and Janney (1917) showed that B. Coli was inhibited in urine with a pH of 4.6 — 5.0, there have been attempts at curing infections by increasing the acidity of the urine. Drugs were first tried to produce this effect, but were found ineffective in rendering the urine sterile and thus obtaining a complete cure; there was always a ghost of

persistent and resistant pyuria haunting these cures. In 1931 Helmholtz and Clark of the Mayo Clinic, after noting that the urine of epileptics on a ketogenic diet, and diabetic urine remained sterile after standing for days, independently introduced the ketogenic diet for the cure of urinary infections. Fuller showed that the active principle of this diet was laevulo beta oxybutyric acid.

Rationale:

The ketonuria was produced by giving a high fat diet. A typical ketogenic diet is: carbohydrate 15 grams, protein 0.3 gm. per lb. body-weight and fat in sufficient quantity to make up the caloric requirements. The ketosis was produced by administering too little carbohydrate for complete oxidation of the fats, with the result that ketone bodies were produced. The results produced by ketogenic diet therapy were excellent and indicated a great advance in therapy had been made, but there were several objections to its use both from the patient's and the physician's viewpoints.

Objections and Contra-indications to the Ketogenic diet:

1. The diet is definitely contra-indicated in cases with diabetes, cholecystitis, poor renal function, peptic ulcer and tuberculosis. Some authorities also include high fever, but many, (including the Victoria General Hospital), used it successfully in these cases.

2. Rigid supervision of the patient and expert administration of the diet by a trained dietitian was necessary. These conditions forced hospitalization of the patients who, with chronic infections, were usually not ill enough to appreciate its need. Besides hospitalization, the added necessity of employing the services of a trained dietitian removed it from the ken of the small hospital, so that it was only available to those patients and doctors in contact with a large institution. Thus the country patients and practitioners were excluded from its benefits.

3. To be effective it had to upset the physiological state of the patient. It could not be continued for long periods and necessitated the addition of yeast to avoid avitaminosis.

4. Strict adherence to every detail of the treatment was necessary. A 90 per cent adherence was not followed by 90 per cent improvement, but by a 100% failure. It was too delicate a mechanism for general use; even the use of any one of the following upset it: a sweet laxative, a soda fountain drink, fruit, chewing tobacco, milk of magnesia or even an innocent chew of gum!

5. The diet was exceedingly discomforting to the patient; this led to cheating, which was just as disastrous to successful treatment as turning a bull loose in a china shop. The patients were troubled by the inevitable repetition and monotony of the menu which lead to nausea and vomiting. To make a concrete example of the drastic change from the normal diet, it should be noted that the maximum daily amount of carbohydrate allowed in this diet (15 grams) is contained in a good slice of white bread! Again, if the patient showed intolerance to the regime,

evidenced by too great nausea and vomiting, he was starved for a day or two, which was effective, since it increased ketosis by combustion of the body fats, but only "added insult to injury". Such were the difficulties and unpleasantries necessary to effective treatment by the ketogenic diet.

MANDELIC ACID

Discovery and Rationale:

Owing to the objections outlined heretofore, investigators have been working to improve the ketogenic diet, or to discover an efficient and more agreeable substitute. Oxbutyric acid orally was tried, but was ineffective because of its oxidation before excretion in the urine. Rosenheim, in May, 1935, was the first to report any sucess in looking for a substitute. He had, after long and careful investigations with various hydroxy and keto acids, found that mandelic acid was the answer to the problem. This acid was excreted in the urine unchanged and, in the presence of a proper pH, exerted a bacteriostatic effect which compared favorably with that of beta hydroxybutyric acid, the active principle of the ketogenic diet. After due experimentation on dogs, it was found to be non-toxic to man and the required acidity could be produced by oral administration of ammonium chloride.

Helmholtz and Osterberg give an excellent exposition of the purely scientific aspect of mandelic acid therapy in J. A. M. A., March 28th, 1936. They have found that the usual bacilli in the urinary tract are killed by a 0:5 per cent solution of mandelic acid, when the urinary pH is 5.5, and at lower pH's, much lower concentration of the drug is necessary. 80 per cent of ingested mandelic acid appears in the urine in twenty-four hours and the maximum excretion occurs approximately two hours following oral administration.

Bacteriological Considerations:

Mandelic acid varies greatly in its effectiveness against different varieties of pathogenic organisms, which makes the bacteriological examination of the urine a great help to scientific treatment. Its bacteriostatic action is most marked against B. Coli; a recent report showed that in a series of 38 cases infected with this organism, 36 (95%) were cured, proved by a sterile urine, while the other two were greatly improved. Recurrence of infection occurred in a few of these cases but readily yielded to another short course of mandelic acid. Streptococcus Faecalis responded just as readily as B. Coli. B. Proteus is harder to kill because its ammoniacal producing action alkalinizes the urine, but once this difficulty is surmounted it succumbs as a lower degree of acidity than B. Coli. In a series of 6 B. Proteus infections there was only one cure and one improvement. B. Lactis Aerogenes and B. Pyocyaneus infections are a great deal more resistant, although a few strains require only a slightly higher acidity than B. Coli. Staphylococcal infections are also very resistant to treatment, while streptococci are slightly more vulnerable. A point stressed by most observers was that cases negative to culture after treatment are more liable to remain so than those only negative for pus.

Urinary infections all give rise to a common manifestation, pyuria. It is most important that we regard pyuria not as a definite disease, but merely as a sign of an underlying primary pathological condition somewhere in the genito-urinary tract between the urinary meatus and the glomeruli, or even further removed in the case of a "periurinary" condition. French, in his *Index to Differential Diagnosis*, lists 25 causes of pyuria. Hence it is necessary to determine the cause of pyuria and decide whether mandelic acid therapy will be used, curatively, as an adjunct to other treatment such as surgery, or will not be effective at all. If we know that the underlying cause is pyelitis or cystitis, which are by far and away the commonest causes, mandelic acid therapy will probably cure the condition.

Indications:

The indications for mandelic acid therapy are the same as those for the ketogenic diet. There are, however, certain cases where mandelic acid can be used but use of the ketogenic diet is impossible, namely gout, diabetes mellitus, gastric and duodenal ulcer.

(A) For Curative Effect:

Mandelic acid cures, that is, renders the urine sterile to culture, in practically all cases of pyuria when (1) there is no obstruction to urinary flow present, (2) no great loss of renal function is present, (3) when the causative organism is B. Coli, as it is in most cases.

1. Acute Pyelitis:

Only three cases are recorded where acute pyelitis was treated by mandelic acid during the acute stage. One of these cases (Lyon and Dunlop), 'was rapidly getting worse, in spite of thorough alkalinization and was desperately ill when mandelic acid treatment was started". There were no ill effects reported in these cures. It is when the acute exacerbation of pyelitis has been calmed by alkaline therapy, and is just beginning to go into the subacute or chronic stage that mandelic acid seems to be most effective and gives the most dramatic results. The acute cases at the Victoria General Hospital have done just as well as the chronic ones on this treatment.

2. Chronic Pyelitis:

In this condition the use of mandelic acid is very encouraging. Many cases treated over a period of years with alkalinizaton therapy and several in which the ketogenic diet had failed, were cured by a course of mandelic acid.

3. Cystitis:

Mandelic acid is effective in this condition when there is no obstruction and the infection is due to the colon bacillus. In cystitis other bacilli are more often associated than in pyelitis, hence mandelic acid is not as efficacious.

(B) As an Adjunct to Other Treatment:

In these conditions pyuria is secondary to some form of urinary obstruction, or to other causes, which need correction before a lasting cure

is effected. The clearing up of the infection by colon bacillus is reflected early in a definite clinical improvement, that is, the patient feels better, the frequency, fever and pain are lessened. However it must be borne in mind that the condition is not cured. The cure of most of these conditions is surgical, but the use of mandelic acid preoperatively lessens the operative risk, while postoperatively the residual infection is, in a great many cases cured. Mandelic acid is of use as an adjunct to other treatment, in the following conditions with concomitant urinary infection:

Stone of the kidney or bladder
Nephroptosis with kinked ureter
Hydronephrosis
Inoperable carcinoma of the prostate
Cases with suprapubic tubes, retention catheters and sinuses
Prostatic hypertrophy with retention
Cystitis following prostatectomy
Bladder diverticula
Urethral stricture.

Contraindications:

The contraindications for mandelic acid therapy are few and have, owing to the short time the drug has been used, not been fully worked out. The following are the main contraindications, deduced from a survey of the literature:

1. Renal Insufficiency.

All those who have written concerning mandelic acid therapy agree on this point. Lyon and Dunlop state, "Don't persist for a long period in patients suffering from renal impairment, especially the aged in whom albumin and casts make their appearance under treatment". The reason for this is obvious; the badly damaged kidneys can neither secrete a sufficiently acid urine nor concentrate the mandelic acid sufficiently. A clinically demonstrable acute or subacute nephritis does not seem to be a contraindication to the use of mandelic acid. Holling and Platt report a cure of two cases of pyelitis in which there was present concomitantly, nephritis with oedema.

2. Gonorrhea.

This is stated on rather shaky grounds. There is only one case of gonorrhea treated with mandelic acid reported in the literature; this man had a subacute urethritis and a subsiding epididymitis and could not stand the severe urethral irritation. A well-known Halifax Urologist states that while mandelic acid is contraindicated in acute gonorrhea, it is valuable in clearing up post-gonorrheal infections.

3. Tuberculosis of the Genito-Urinary Tract.

In two patients the treatment caused an exacerbation of symptoms, while in two other cases no improvement followed clearing up the secondary infection. It is interesting to note that cases wherein the tubercle bacillus could not be found routinely, often show it after the treatment has been in force for awhile.

RESULTS

Since it is impossible to give case reports in an article of this size, the results have been briefly summarized and condensed in the following tables.

TABLE 1

Investigators.	No. of Cases.	*Cured.	Improved.	Failure.	Duration of Infect. (Av.)	Time to Sterilise Urine. (Av.)	Cause of Failure and Remarks.
1. Rosenheim..	12	4	6	2	27 weeks	10-12 days	1. Woman 4 mos. pregnant, vomiting and uterine pains, stopped treat., ketogenic diet also failed; ill effects, especially nausea and dysuria.
2. Lyon and Dunlop...	16	13	1	2	1½ years	8 days	Treat. stopped because of side effects; B. Proteus, Staphs and Streps, and couldn't get urine acid.
3. Holling and Platt.....	29	24	2	3	1½ years	5 days	Prostatic calculi; died of B. Coli Septicaemia; Tbc bladder and kidney.
4. Carroll et al	50	30	13	7	.....	7 days	Series included many surgical cases. See Table 2.
5. Dolan.....	16	9	2	5	.....	.....	Ammonium mandelate used; Staphs, g. c. and strep viridans.
Totals....	123	80	24	19			
Percentage		65%	20%	15%			

TABLE 2
RESULTS BY BACTERIOLOGICAL CLASSES, CARROL ET AL

Causative Bacteria.	No. of Cases.	Cured.	Improved.	Failure.	Causes of Failure	Remarks.
B. Coli	37	30	7	0	Multiple diverticula and stricture, Bi-lateral pyelonephritis.	Only one treated in acute exaceration.
B. Proteus.....	6	1	1	4	Mostly cases of chronic cystitis.	Cure was a case of Chronic pyelitis.
Staphylococci..	7	1	4	2	Nephrolithiasis; postoperative resection of prostate.	Pelvic vesical sinus made sterile to culture.

*Cured—Urine Sterile to culture on discharge, as reported in the literature.

The clinical improvment was the most striking and earliest result. It was evidenced by improvement in the symptoms, headache, backache and frequency (especially nocturnal), which were greatly diminished

within a few days of starting treatment. Carroll's 37 cases of B. Coli infection included acute and chronic pyelitis, vesical diverticula, nephroptosis, renal calculi and prostatic hypertrophy with retention and cystitis. All these became negative to microscopical examination and only seven showed positive cultures.

Table 2 shows how effective mandelic acid was in the cure of B. Coli infections. There was not a case of failure and a complete cure in 79 percent of cases, while the rest were clinically improved—all except two were negative to microscopical examination. Of seven cocci infections, one was cured and four improved. In most cases of failure with mandelic acid, ketogenic diet has also failed.

From Table 1 it is seen that in this review of 123 cases of urinary infection, 80 (65%) were cured, and 24 (20%) were improved, while the treatment failed in only 19 cases (15%). Cook and Buchtel report a series of 92 cases, (not included in Table 1 because of insufficient data), in which 77 were rendered sterile by sodium or ammonium mandelate treatment. Therefore in the total 215 cases reported, a complete cure was obtained in 157 or 73%. One must bear in mind that this series of cases includes many conditions in which mandelic acid therapy was later found to be ineffective, or contraindicated. Therefore if mandelic acid is used only for cases where it is indicated, the percentage of cures should be much higher.

There were a few instances of recurrence of infection in these cases, but most of them yielded to another short course of mandelic acid. It is stated by a number of the V. G. Hospital staff that recurrences are more common in mandelic acid therapy than with the ketogenic diet. The striking feature in numbers 2 and 3 of Table 1 (the English cases) was the previous duration of infection, averaging 1½ years, yet most of these yielded to treatment in 5 to 8 days! One of these infections of 8 years duration was cured in 8 days!

Administration:

The dose of mandelic acid, in any form is three grams (gr. 45) four times daily. When it is administered as sodium mandelate or as mandelic acid, it is also necessary to give eight grams (2 drachms) of ammonum chloride daily in divided doses. This last dosage cannot be rigidly set for every case, but must be given in doses sufficient to cause a urinary acidity of pH 5.3. Lyon and Dunlop, and Holling and Platt report that a satisfactory pH was obtained in most cases with half this dose.

Rosenheim gave mandelic acid in the following way:

R

Mandelic Acid 45 grains
Soda Bicarbonate 24 grains. Just enough to neutralize.
Syrup of Lemon 1 drachm
Water to 1 ounce

One ounce in water four times a day.

He supplemented this by giving 8 one gram cachets of Ammonium Chloride a day.

Holling and Platt prescribed sodium mandelate in the following way:

R
Sodium Mandelate 50 grains
Syrup of Orange 1 drachm
Water to 1 ounce
In water four times daily.

This was preceded by:

R
Ammonium Chloride 30 grains
Liquid extract of liquorice 15 minims
Water to 1 ounce.
Four times daily.

The fluid intake was restricted to one quart daily, unless thirst was complained of, when more fluid was allowed.

Carroll et al used a similar formula to Rosenheim, but started with the mandelic acid after a pH of 5.5 was obtained by means of the acid ash diet and 1 gm. ammonium chloride four times a day. He pointed out that persistence of an alkaline urine was often due to inclusion in the diet of orange or lemon juice, spinach, beans, molasses or olives.

Ammonium mandelate was used in four of Holling and Platt's cases; all were cured and a proper urinary pH was reached in every case but one without the use of any urinary acidifier such as ammonium chloride. Dolan reports 19 cases in which ammonium mandelate was used without any urinary acidifier, (See Table 1). Cook and Buchtel used this preparation in 17 cases with 16 cures resulting and only one required ammonium chloride. They also used ethanolamine mandelate on five cases; three of these became negative to culture and one required ammonium chloride. When satisfactory acidity could not be gotten by means of ammonium chloride they used HCl orally and in a few found it necessary to use the ketogenic diet along with the mandelate treatment.

Mandelic acid cannot be given in pure form because it is a gastric irritant. Ammonium chloride is especially nauseous to some patients, even causing vomiting. Even when given in capsules it may, in these individuals, cause an unpleasant after taste. Ammonium mandelate therefore has the advantage over sodium mandelate in that it renders unnecessary the unpleasant taking of ammonium chloride in most cases. Ammonium mandelate is available in the following proprietory preparations, Amdelate (Abbott), Mandelix (B.D.H.) and a new preparation by Parke Davis.

The great advantage to the patient in mandelic acid therapy is that they can carry on their usual work unless physically incapacitated by their disease. A close check up is necessary daily on the pH. This can be done with a variety of indicators which change color at pH. 5.3,—methyl red solution and two paper indicators, chlorphenol and nitrazine. Focal infections should be routinely checked and one must be certain that the condition is not caused by the tubercle bacillus. Treatment should not be continued more than three weeks.

Unpleasant Side Effects During Treatment:

Mandelic acid does not seem to be very toxic to the body as is shown by the following facts. Helmholtz and Osterberg gave 700 c.c. of 1 percent Mandelic Acid intravenously to a dog in 7 hours; the blood urea was raised and urine urea lowered, but these came back to normal in three days. This shows that it only temporarily lowers renal function. This fact was con-

firmed in humans. One patient was given 360 grs. of Ammonium Chloride a day, which produced a true acidosis with nausea and vomiting, but no serious or permanent damage.

The undesirable effects occuring in a few cases during treatment with mandelic acid may be listed as follows:

Urinary:
Occasional casts, hyaline and granular
Dysuria
Increase of albuminuria
Red Blood Cells

Gastro-intestinal:
Indigestion
Nausea and vomiting
Diarrhoea

Sensory: Buzzing in the ears; Temporary deafness; Giddiness.

That these effects are uncommon is concluded from the fact that in the 123 cases reviewed there were only 19 showed even slight ill effects. Concerning the urinary symptoms,—they do not seem to be of grave import unless marked, since in the most cases they were ignored and the infection cured. They should, however, be watched for carefully when there is renal insufficiency. The blood and casts in the urine are thought to be due to the high acidity in the urine, rather than the mandelic acid. Mandelic acid has been given daily over a period of a month without producing any albuminuria, therefore it is not a general renal irritant.

The sensory symptoms in all cases were trivial and in no way interfered with treatment.

The gastrointestinal symptoms were the most troublesome. In two or three cases, it was necessary to stop the treatment because of nausea and vomiting.

All these ill effects seem to have been much more prevalent in the earlier trials of mandelic acid. Cook and Buchtel report that less than one percent of their 92 cases had nausea and vomiting; 10 percent had slight diarrhoea. In a few with 8-10 stools a day, treatment was stopped and later continued without any ill effects. Carroll et al reported no toxic effects or impairment of function in 50 cases. Dolan, using ammonium mandelate on sixteen cases, reported two cases with ill effects; one, with renal tuberculosis had haematuria and exacerbation of all symptoms, while the other, a case of gonorrhea, had severe urethral irritation.

It seems quite likely that most of these effects are due to the ammonium chloride used, especially the gastric symptoms. This statement is made because the nauseating effects of ammonium chloride are well known and also because of the fact that they are less common in the cases where ammonium mandelate was used, obviating the use of ammonium chloride. Some of these effects, especially the sensory are due to the acidosis produced.

Deductions and Summary:

Dolan in J. A. M. A. states, "While mandelic acid therapy may supplant treatment with the ketogenic diet in 75 percent of cases, it cannot

replace it entirely— In conjunction with the ketogenic diet, mandelic acid will be extremely helpful. Often with the diet alone, we are able to gain satisfactory acidity, but the concentration of beta-hydroxybutyric acid is not great enough to render the urine bactericidal. It is in this type of cases that a combination of the ketogenic diet and mandelic acid will prove most valuable."

The greatest feature of mandelic acid therapy is its wide applicability to all members of the profession, whether they are attached to large hospitals or are general practitioners, playing a lone hand. Many Halifax clinicians have stated that they have had excellent results using this treatment. It has replaced the ketogenic diet in treatment of most urinary infections at the Victoria General Hospital. In any doctor's hands it will prove a very efficacious remedy,providing the few simple rules necessary to its proper use be applied.

Summary:

The advantages of, and the important points in mandelic acid treatment are:

1. The dose is 45gr. of mandelic acid, (in any form), four times daily.
2. One must maintain the urinary acidity at pH 5.3.
3. Drugs, some fruit juices and foods that tend to alkalinize the urine are contraindicated during treatment.
4. Fluids should be restricted to one quart daily.
5. Its curative effect is greatest in infections due to B. Coli where there is no urinary obstruction. Cocci infections are quite resistant.
6. It is often valuable as an adjunct to other treatment, when these conditions do not exist.
7. Its continued use is contraindicated where there is renal insufficiency.
8. It cures many cases where the ketogenic diet fails.
9. Ammonium mandelate seems to be the pleasantest form to use.
10. It is practicable for every practitioner to use.

BIBLIOGRAPHY

Ketogenic Diet:

Winfield, G. A., N.S. Med. Bull. Mar. 1936.
V. G. Hospital Ketogenic Diet—Courtesy of Miss E. H. Todd.

Mandelic Acid:

Rosenheim, M. L., Lancet, May 4, 1935.
Holling and Platt, Ibid, Apr. 4, 1936.
Lyon and Dunlop, Brit. Med. Journ., Dec. 7, 1935.
Helmholtz and Obsterberg, J.A.M.A., Nov. 28, 1936, P. 1794.
Carroll, Lewis and Kappell, Ibid, Nov. 28, 1936, P. 1796.
Cook and Buchel, Ibid, Nov. 28, 1936, P. 1799.
Dolan, L. P., Ibid, Nov. 28, 1936, P. 1800.
Handfield-Jones, R. M., Infections of the Urinary Tract, Practitioner, Dec. 1936.

"Medicine arose out of the primal sympathy of man with man; out of the desire to help those in sorrow, need and sickness."—From "Evolution of Modern Medicine" *Sir William Osler.*